REMARKS

Claims 1 to 12, 15, 32, 35, 36 and 37 are pending in the present case of which claims 1, 32 and 35 are in independent form. Claims 13, 14 and 26 to 29 are cancelled. Claims 16 to 25, 30 to 31 and 33 to 34 are withdrawn from consideration.

Claim 1 was amended to refer to "sequences" as well as partial sequences. Support for this amendment can be found throughout the specification, but also in the dependent claims such as claim 7, in particular 9, 11 and 12.

Claim 35 was amended to correct an error in SEQ ID NO 7.

Response to Election/Restriction

Applicants kindly request that the Office considers searching the following species after the elected species (SEQ ID NO:3), namely, SEQ ID NO: 1, SEQ ID NO:2 and SEQ ID NO:4. Applicants also kindly request that the Office considers searching "dilatative myocardiopathy" as the next disease species after the elected species.

Objections to the Drawings

Applicants submit herewith an "Replacement Sheet" for Figure 1, now referring to "Figure 1" as requested by the Office.

Objections to the Disclosure

The Office noted that on page 12, in the paragraph starting on line 9, the loop I and II information for ß1 myocard was listed as identical sequences. The loop I information on line 11 for ß1 myocard was corrected to show sequences which correspond those of loop I of closely related peptide ß1 DCM in line 9. Applicants submit that the person skilled in the art would have readily recognized the mistake and would have known how to replace it, in particular in view of the equivalence of the loop II information for ß1 myocard and ß1 DCM.

In response to the objections regarding the lack of SEQ ID NOs on pages 12 and 13, the appropriate SEQ IDs have been introduced.

Objections to the Claims

Claims 8 has been cancelled rendering the respective objection moot.

Claims 12, 32 and 35 has been amended to introduce the appropriate SEQ ID NOs.

Rejections under 35 USC §112, second paragraph

The Office rejected in claim 1, step b) "the precipitated fraction" and in step d) "the material" for lack of antecedent basis. The Office considered the phrase "particular one" as rendering the claim indefinite and suggested to replace "whereby" with "wherein" in step e).

In response, applicants eliminated the antecedent basis issues, eliminated the phrase "particular one" and replaced "whereby" with "wherein" as suggested by the Office.

On page 4, the Office expressed the opinion that claim 1 was incomplete for omitting essential steps between (1) the "denaturing agent" of step a) and the "precipitated fraction" of step b), (2) between "incubating" of step c) and "washing" of step d) and (3) "enzyme reaction or color reaction of step f) and the "marked" anti- IgG antibody in step e).

Applicants have amended the claim as set forth herein to address this rejection. In particular, applicants have introduced amendments suggested by the Office in the context of the enablement rejection (page 7 of the Action) and have, based on language already present in the claim, amended the claim to improve its clarity.

Claim 1 has also been amended to clarify that the detection is for diagnostic purposes. Support for this amendment can be found throughout the specification, including in original claim 1 and on page 3, first paragraph.

Also on page 4, the Office rejected in claim 6 the phrase "is used in the detection of" [disease] as not corresponding to the wording of the preamble.

In response, applicants have amended claim 6 as suggested by the Office.

On pages 4 and 5, the Office rejected claim 6 as potentially double reciting the disease

"dilatative cardiomyopathy" also as "dilatative myocardiopathy".

While these diseases in fact share loop I and loop II peptides, applicants note that due to the divergent nomenclature used in the clinical practice small differences may exist and thus would like to retain both nomenclatures in the claims to account for any of these differences.

On page 5, the Office rejected claim 9 as indefinite and suggested to replace in each line commencing with "in the case of" the term "are used" with "is detected".

In response, applicants have amended the claim accordingly.

Also on page 5, the Office expressed the opinion that in claim 10, nexus is missing between the "denaturing agent" and the "precipitated fraction" of claim 1 and the manner the "autoantibodies are concentrated or purified." The Office also noted a discrepancy of the wording of the claims relative to the preamble of claim 1.

Applicants have amended claim 1 and claim 10 to address the issue as raised by the Office incorporating the suggestions that the Office made in context of the enablement rejection of, in particular, claim 1 (page 7 of the Action).

In claim 11, applicants addressed the antecedent basis issue ("the method for concentrating and purifying") raised by the Office by changing the dependency of this claim to claim 10 and changing the designation a) to d) to avoid confusion in view of claim 1. Also, applicants have clarified the relation between former step b) (now ii)) and step c) (now iii) by specifying how the peptide is coupled to the carrier. Support for the amendments is provided throughout the specification, but in particular in the Example, more in particular the first paragraph on page 25 and the wording of original claim 11.

In claim 12 and 32, the wording of the Markush group was adjusted in accordance with the Office's suggestions.

Claims 13 and 14 were canceled and the 35 USC §112, second paragraph rejections of these claims are therefore now moot.

Claims 32 and 35 have been amended to describe the methods claimed in more detail to provide process steps to better comply with 35 USC §101.

Rejections under 35 USC §112, first paragraph

On pages 6 and 7, the Office rejected claims 1 to 15 under 35 USC §112, first paragraph, stating that, while the specification is enabling for the case in which one uses an agent for precipitating autoantibodies, does not reasonable provide enablement for the case in which one uses a denaturing agent, in step a) of claim 1.

The Office considered in particular the scope of "denaturing" agent as extremely broad and suggest the term "a precipitating agent for autoantibodies" as disclosed on page 6, second full paragraph of the specification.

In response, applicants have amended the claim accordingly (Note: applicants used the term "an agent for precipitating autoantibodies" as used by the Office on the bottom of page 6 of the Action).

On pages 7 and 8, the Office rejected claims 1 to 15 under 35 USC §112, first paragraph, stating that, while the specification is enabling for the case in which the peptide used in step b) of claim 1 is a peptide comprising biotin, does not provide enablement for the case in which step b) of claim 1 is a peptide lacking biotin in particular in view of the recitation of avidin or streptavidin in c).

In response, applicants have provided a more consistent wording of the claim in accordance with the Office's suggestion on page 8 of the Action. As pointed out by the Office, the particular language is supported by, e.g., the paragraph spanning pages 5 and 6 of the specification.

On page 8, the Office rejected claim 15 under 35 USC §112, first paragraph, as failing to comply with the written description requirement. The Office expressed the opinion that the claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of claimed invention. In particular, the Office expressed

the opinion that applicants were not in possession of the genus of peptides that have been "modified by means of deletion, addition, substitution, translocation, inversion and/or insertion."

In response, applicants have amended the claim to delete the reference to "translocation", "inversion" and "insertion."

With regard to the written description of deletions, additions and substitutions, applicants would like to refer the Office to page 8 of the specification, where applicants describe the skill in the art at the time of filing of the application. Here the specification refers, among others, to PNAS USA 1998, Oct. 13; 9521:12179-84 and WO 99/62933, which describe advances in peptide design using so called "seed peptides" that display the desired activity. This work is in particular directed at a peptide that fully prevents the positive chronotropic effect of anti- ß1-adrenoreceptors autoantibodies from the serum of patients with idiopathic DCM. Based on the information provided, using these "seed peptides", useful novel artificial epitope sequences could be generated that mimicked the natural linear epitope sequence and showed almost equivalent and occasionally even better result *in vitro* than the respective seed peptide (see Fig. 6 of the PNAS publication attached and relating discussion).

Applicants submit that, in a written description analysis, the specification should be considered from the standpoint of one of skill in the art at the time the application was filed (see, e.g., *Wang Labs. v. Toshiba Corp.*, 993 F.2d 858, 865, 26 USPQ2d 1767, 1774 (Fed. Cir. 1993)). Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement. Information which is well known in the art need not be described in detail in the specification. See, e.g., *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986) [MPEP 2163].

Applicants submit that, in view of the general knowledge in the art as exemplified by the references as referred to in the specification, an adequate written description is provided for deletions, additions and substitutions as claimed.

Also, applicants submit that it was well-known to those skilled in the art, at the time of the application, that some amino acids have analogous physicochemical properties so that these

amino acids advantageously can be replaced by each other as specified in the first full paragraph of page 8 of the specification.

The 35 USC §112, first paragraph rejections of claims 13 and 14 on page 9 of the Office Action are moot in view of the cancellation of these claims.

Rejections under 35 USC §102/103

On pages 9 to 11, the Office rejected claims 32 and 35 under 35 USC §102(b) or (e) as anticipated by, or in the alternative, under 35 USC §103(a) as obvious, over either Wallukat et al. (1995) (hereinafter "Wallukat') or Rönspeck et al. (WO01/21660 or US Patent 6,994,970) (hereinafter "Rönspeck").

In particular the Office expressed the opinion that Wallukat teach the peptide sequences which constitute the dominant auto-antibody- reactive epitopes of the first and second extracellular loops of the ß1 adrenoreceptor. The Office noted that Wallulat states that earlier investigators have shown that the sera of DCM patients contain autoantibodies that react with peptides derived from the first and second extracellular loops of the ß1 adrenoreceptor.

Rönspeck is said to teach the same epitopic sequences as Wallukat, but including flanking sequences. Rönspeck is also said to have conducted an ELISA assay for autoantibodies in the sera of DCM patients.

The Office noted in the context of claims 32 and 35 that these claims do not require any particular immunoassay format, and do not require the use of any particular reagent, except for one or more of the recited peptides.

Claims 32 and 35 have been amended to specify the diagnosis/monitoring of specific diseases (claim 32) or the detection of specific autoantibodies (claim 35) to address the anticipation rejection. The Office is therefore directed to the non-obviousness discussion below.

On pages 11 to 13, the Office rejected claims 1 to 8, 10 to 13 and 15 under 35 USC §103(a) as obvious over either Wallukat et al. (1995) (hereinafter "Wallukat') and Rönspeck et al. (WO01/21660 or US Patent 6,994,970) (hereinafter "Rönspeck"), both in view of US Patent 4,468,470 to Aalberse (hereinafter "Aalberse").

The Office acknowledged that neither Wallukat nor Rönspeck teach the precise method by which they conduced assays for autoantibodies in the sera of DCM patients.

However, the Office expressed the opinion that Aalbrese teaches a format for conducting an assay for antibodies against an antigen, in which soluble antigen coupled to biotin (or a hapten) is incubated with a body fluid sample possibly containing antigen-reactive antibodies. Following incubation, the sample is then added to an insoluble/carrier/solid-phase bound avidin (or anti-hapten antibody). Any complex formed is detected by an labeled anti-Ig antibody. The Office referred in particular to col. 2, line 1 to col. 3, line 3 of the reference.

The method presently claimed in claim 1 is directed at a diagnostic method for detecting disease-associated autoantibodies, which are directed at G protein-coupled receptors.

Wallukat et al., J Mol Cell Cardiol. 1995;27:397-406 discloses four peptides (EYGSFF, SFFCEL, ARRCYND und PKCCDF) and their use in *in vitro* experiments for the inhibition of the positive chronotrophic effects of anti-ß1- andrenoreceptor autoantibodies in cultivated, neonatal rat-cardiomyocytes. Wallukat also discloses the binding of those peptides to autoantibodies.

Wallukat does not disclose the use of these peptide for a diagnostic method.

Rönspeck discloses the use of some of the peptides for the production of pharmaceuticals. Rönspeck also discloses in column 8, lines 11 to 23 an assay for DCM related autoantibodies using the assay described in the above cited Wallukat reference.

As Wallukat, Rönspeck does not disclose the use of these peptides for diagnostic purposes.

At the time the invention was made, DCM was, for example, diagnosed using echocardiogram and X-ray analyses.

Applicants respectfully submit that the person skilled in the art would not have been motivated, let alone would have had a reasonable expectation of success, to deviate from the

established tests to provide peptides, which with autoantibodies, in particular autoantibodies contained in a body fluid, can be detected, in particular for diagnostic purposes.

A diagnostic method serves the purpose to determine whether an organism is indeed sick and if so, what it became sick from. Diagnostic methods generally aim at a positive diagnosis, where the determined anamnestic data and/or findings are specific for a certain disease state. The person skilled in the art knows that the number of false positives has to be minimal, since otherwise, among others, wrong or superfluous treatment might ensue.

The following example shall serve as an illustration:

The example assumes that about 100 in 10000 people suffer from a particular disease. A diagnostic method aims at diagnosing the existence of the disease, but generally provides 1% of false positives. That means, in this example, that there is a false positive result in one percent of 99 of 9.900 tests. Due to the low disease rate, 198 of 10000 tested are diagnosed as sick, while only half of them are indeed sick (and that only under the assumption that there are no false negatives). Thus, even though the test has a sensitivity and specificity of respectively 99%, the diagnosis "sick" is only accurate in 50% of all cases, i.e., a person that receives the diagnosis sick is in 50% of all cases not sick.

The person skilled in the art, who is faced with the task to provide a diagnostic tool for, e.g., DCM, knows that in the context of autoimmune diseases, even though they have a common pathogenetic basis, the situation is considerably more complex than in the example provided above. Thus, in the case of an autoimmune disease, the person skilled in the art would aim at a higher specificity to obtain meaningful diagnostic results.

Wallukat discloses that only 58% of the persons tested with DCM have antibodies against loop 1 of the receptor. Wallukat refers also to an earlier study in which the percentile was only 27%.

The person skilled in the art would reasonably conclude that patients with DCM appear to be very heterogeneous as far as potential autoantibodies are concerned. Even if the patient has autoantibodies, those would be expected to be directed against different structures (loops) of the epitope area. In view of Wallukat, the person skilled in the art would reasonable conclude that

only a third of patients having DCM display autoantibodies, which, in addition, are also directed at different loops of the receptor, rendering the claimed peptides ill suited for in particular diagnostic detection of autoimmune diseases.

The experiments of Wallukat further show that it is possible to bind a conglomerate of antibodies with the disclosed peptides. However, this, per se, is insufficient for a diagnostic approach. In diagnosis, the specificity of the peptides is the most important criteria. However, Wallukat provides no data regarding specificity (among others, since he seeks to answer a quite different question, in which specificity is a lesser concern).

The person skilled in the art would also interpret Wallukat as suggesting that the peptides do not exclusively bind disease associated autoantibodies, thus rendering any test based on them prone to false positives. In particular, Wallukat tests the autoantibodies via their effect on myocytes of rats. It was assumed, if the beating frequence increased, autoantibodies that bind the anti-$ß_1$-adrenoreceptor were present. However, the peptides disclosed in Wallukat are themselves negative chronotropic, so that the results obtained have no real informative value as to the presence of autoantibodies. "Negative chronotropic" means that the peptides themselves, are able to decrease the beating frequence, which in turn means that the peptides directly interact with the receptors. These interactions with the receptor show, according to Wallukat, that the peptides engage in unspecific binding. This unspecific binding with the receptor from which the peptides originate would further dissuade the person skilled in the art to use then as binding agents for autoantibodies, in particular for diagnostic/detection purposes, since, next to the autoantibodies, other structures would be bound by the peptides.

The results of experiments with multiple peptides were, according to Wallukat, not homogenous (see page 402, paragraph 2). The different peptides had, in different patients, different results, which further advocates against their use in diagnosis, which generally requires uniformity of results among the subjects tested.

According to the cited state of the art, only 27 to 50% of patients with DCM display autoantibodies. In addition, autoantibodies can be detected in healthy persons. Thus, a testing of 100000 patients would, according to the state of the art, result in 5000 false positives and 30000 patients having the DCM would not be diagnosed as such.

Thus, for the reasons stated above, but in particular since the prior art supported that the

autoantibodies would not be present in all DCM patients (in particular in combination with unspecific binding properties discussed above), the person skilled in the art would have little, if any, motivation to use the peptides of the present invention in detection or diagnosis.

In the case of other diseases such as Chagas' myopathy and myocardias, the prior art provides little indication as the stability of the autoantibodies, providing little incentive to the person skilled in the art to use the claimed peptides for detection of the respective autoantibodies and their use in the diagnosis of these diseases.

Rönspeck disclosure does, for the purposes of the presently claimed invention, not add anything to the disclosure of Wallukat. Rönspeck's disclosure in column 8, lines 11 to 23 of an assay for DCM related autoantibodies, is, as the Office noted, the assay described in the herein discussed Wallukat reference.

In view of the properties of the peptides as discussed by Wallukat and Rönspeck, applicants respectfully submit that the person skilled in the art would have had little motivation to use these peptides in diagnosis and detection. In particular, such a person would have had little motivation to combine the teachings of Wallukat or Rönspeck with the teachings of Aalberse to arrive at the invention as presently claimed with any expectation of success.

No fee is believed to be due in addition to the extension of time fee paid herewith. However, the Commissioner is authorized to charge or credit deposit account no. 50-3135 as required. Any petition that may be required for the consideration of this response is herewith respectfully requested.

Respectfully submitted,

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